Immunity
Review

Cell Surface Signaling Molecules in the Control of Immune Responses: A Tide Model

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A large numbers of cell surface signaling molecules (CSSMs) have been molecularly identified and functionally characterized in recent years and, via these studies, our knowledge in the control of immune response has increased exponentially. Two major lines of evidence emerge. First, the majority of immune cells rely on one or few CSSMs to deliver a primary triggering signal to sense their environment, leading to initiation of an immune response. Second, both costimulatory CSSMs that promote the response, and coinhibitory CSSMs that inhibit the response, are required to control direction and magnitude of a given immune response. With such tight feedback, immune responses are tuned and returned to baseline. These findings extend well beyond our previous observation in the requirement for lymphocyte activation and argue a revisit of the traditional "two-signal model" for activation and tolerance of lymphocytes. Here we propose a "tide" model to accommodate and interpret current experimental findings.

Introduction

All immune cells, including those participating in the innate and adaptive immune response, have evolved to express distinct cell surface receptors or ligands to sense and respond to environmental cues. These cell surface signaling molecules (CSSMs) are vital for differentiation, recognition, and cellular function. Many cell types consistently monitor the dynamic environmental stimuli through their unique receptors to recognize specific changes. For example, a specific T cell receptor (TCR) binds a major histocompatibility complex (MHC)-peptide structure on a professional antigen-presenting cell (APC). This TCR transmits an antigenic signal, initiating the downstream signaling pathways of an immune response (Smith-Garvin et al., 2009). APCs also respond to changes in their surrounding environmental stimuli using toll-like receptors (TLRs) to identify potential pathogens (Palm and Medzhitov, 2009). Natural killer cells (or NK cells) utilize natural cytotoxicity receptors (NCRs) to recognize changes on target cells caused by viral infections or stress (Lanier, 2005). High-affinity IgE receptors on mast cells contribute to immune detection and surveillance by identifying allergen-IgE complexes (Sayed et al., 2008). Therefore, immune cells utilize these receptors to transmit an initial signal to turn on the immune response.

For years immunologists have sought to understand the mechanisms of antigen-specific immune responses and the versatile nature of antigen receptors on the surface of lymphocytes. With the attempt to produce a cellular model incorporating the theory of self and nonself discrimination, Bretscher and Cohn were the first to propose a two-signal model to account for B cell tolerance induction (Bretscher and Cohn, 1970). Later this model was extended and applied to T lymphocytes by Lafferty, Schwartz, and colleagues (Lafferty and Cunningham, 1975; Mueller et al., 1989).The two-signal model explains why lymphocytes are only partially activated or even unresponsive after exposure to Signal 1 from antigen-receptor. Only after exposure to a second, costimulatory cell surface signal does full activation of the lymphocyte occur (Lafferty and Cunningham, 1975). Further experiments revealed a molecular identity for the costimulatory signal (also called Signal 2): the CD28-CD80 interaction (Linsley et al., 1990). Since then, the two-signal model has gained increasing experimental support, contributing to our understanding of lymphocyte activation.

The last decade has witnessed dramatic progress in the identification and characterization of CSSMs, largely due to the completion of the human genome project. More than 4000 molecules have been identified as potential CSSMs, based on similarities in their transmembrane protein structure, along with their signature intracellular and extracellular domains (Lander et al., 2001; Venter et al., 2001). A group of these CCSMs have been functionally characterized, giving new perspectives on the regulation of immune responses and translating to the clinic new therapeutic treatments of human disease. Studies characterizing the role of individual immune cells and their specific type of immune responses have revealed several large gene families that provide critical signals in immune cell activation, including tumor necrosis factor (TNF), immunoglobulin (Ig), G protein-coupled receptor (GPCR), and the lectin receptor family (i.e., Siglec, Dectin, DNGR-1, DC-SIGN, etc.). In this review, we propose a comprehensive "tide" model to bridge the gap that exists between our current knowledge of specific immune cell regulation and how the complex, downstream, multicellular immune response is regulated and controlled by CSSMs.

Rationales for the Revision of the Two-Signal Model

Our understanding of T lymphocyte activation has been profoundly influenced by the "two-signal model" in which costimulation provided by "Signal 2" is necessary for optimal activation of lymphocytes. Functional analyses indicate that CSSMs are not only costimulatory but also coinhibitory (Greenwald et al., 2005). Importantly, expression of these coinhibitory molecules is often induced de novo or upregulated upon T cell activation in the presence of costimulation, indicating a negative

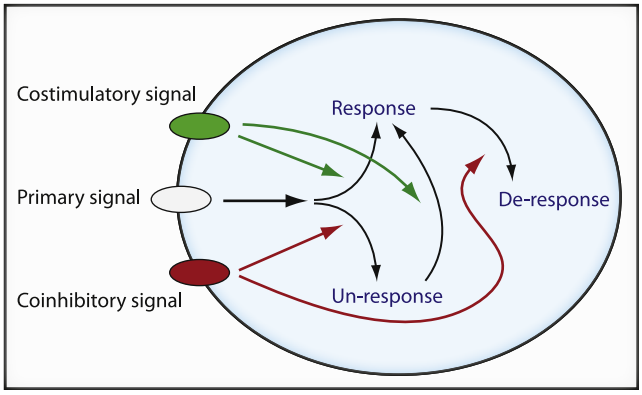

Figure 1. The Tide Model for the Control of Immune Response
We define the primary signal as a triggering signal that is initiated by specific binding of ligand to its receptor (R) on immune cells. The primary signal selects and/or marks the cells but is not sufficient to induce a biologically significant "Response" such as phosphorylation of the receptor or the receptor complex. In the absence of cosignals, the primary signal normally does not decide the direction and magnitude of a cellular response. The cosignals, which could be either costimulatory or coinhibitory, are modulators of the primary signal and could decide the directions and magnitude of a cellular reaction. The primary signal could either induce "Response" when costimulatory signal is dominant or trigger "Un-Response" in the presence of dominant coinhibitory signal. With a strong far-reaching coinhibitory signal, even an initial "Response" could be terminated ("De-response"). Similarly, a strong costimulatory signal may also reverse "Un-response" to "Response." It is worth noting that a "Response" does not always lead to activation of an immune response. For example, a "Response" of regulatory T cells often suppresses immune response while the "Response" of CD25-FoxP3-CD4+ T cells may enhance an immune response. With such tight control of cosignals, all cellular response will have a rise-and-fall pattern like the tide.

feedback response of the immune system. Genetic ablation of these coinhibitory molecules in mouse models often leads to various autoimmune diseases associated with overactive T cell responses (Chen, 2004), demonstrating the indispensible role of coinhibitors in in vivo T cell tolerance induction. Therefore, although the TCR signal is essential and required for the selection and initial triggering of T cell responses, it is often the cosignal that dictates the outcome of a T cell response, including both activation and tolerance. Additionally, nearly all immune cells including NKT cells, NK cells, γδ T cells, macrophages, dendritic cells (DCs), monocytes, and mast cells (besides T and B cells) also have been shown to have similar requirements for a primary triggering signal (Signal 1- like), and ample experimental data demonstrate that CSSMs are present on these cell types and are able to modulate and fine tune their responses.

The "Tide" Model

Left unchecked, uncontrolled inflammatory immune responses are dangerous to the host; therefore, under this hypothesis the necessary immune components and the resulting inflammatory responses are tightly controlled to limit or avoid excess damage to the surrounding tissue. Here we propose a new tide model of immunity that incorporates our current molecular understanding of an immune response (Figure 1) and provides additional insight into both innate and adaptive immunity. In this model, we define primary signal as the initiator of specific immune cells reacting to extracellular stimuli. Meanwhile, the cosignals, either costimulatory or coinhibitory, are modulators that decide the direction and magnitude of the immune response. The characteristics of this self-feedback, tide signal model are outlined below.

First, the role of primary signal is extended to include a broader, more intricate function in immunity, spreading beyond its current activity through TCR and BCR to include initiating a cascade of activation or deactivation on all immune cells during both innate and adaptive immune responses.

Second, primary signal is the initiator, but primary signal itself does not decide the fate of the immune response. Primary signal is received by the receptors on certain immune cell types; then these cells can induce several early downstream biochemical signaling events. However, it is the cosignals that determine the overall outcome of the immune response.

Third, cosignals include signals with stimulatory function (costimulator) as well as that with inhibitory function (coinhibitor). While a costimulatory signal is required to optimize an immune response, the coinhibitory signal is often induced and triggered by primary signal together with a costimulator, thus serving as a strong negative feedback signal. Therefore, we use "tide" to describe the rise and fall of immune response due to interplay of these signals.

Finally, cosignaling molecules are highly diverse in abilities to monitor and control immune cell responses. The expression of cosignaling molecules is differentially and tightly regulated through every stage and location of immune cell activation. They transduce signals through a series of cosignaling pathways. In addition, the nature of individual cosignaling molecules determines its preferential participation in one or more functional aspects of immune cell activation.

Signal 1 and Cosignals for Immune Cell Subsets

Each cell type bears different "recognizing" receptors for primary signal, and signaling through these receptors is very distinct (Figure 2). As for cosignaling molecules, a lot of them are shared among several cell types while some are uniquely present on certain cell types (Table 1).

αβ T Lymphocytes

T lymphocytes are the essential components for adaptive immune responses. αβ T lymphocytes constitute 98% of total T cells. T cells represent the cell type that has been most comprehensively and extensively studied with regard to the role of cosignals. In addition to CSSMs, cytokines, such as interleukin-12 (IL-12), transforming growth factor-β (TGF-β), and IL-6, are crucial for further differentiation of T cells, especially $CD4^+$ T helper cells, though the role of cytokines as cosignals is beyond the scope of this review.

Primary signal for conventional T cells is mediated through TCR engagement. Conventional T cells carrying the αβ TCR recognize small antigenic peptides presented in the groove of the self major histocompatibility complex (MHC). As a result of this recognition, TCR complexes aggregate on T cell surfaces to form stable contacts resulting in the formation of immunological synapses on APC (Huppa and Davis, 2003). Early intracellular signaling, following TCR engagement involves the activation of Src (Lck and Fyn) protein tyrosine kinases (PTKs), leading to the phosphorylation of CD3-localized immunoreceptor tyrosine-based activation motifs (ITAMs). Subsequently, the PTK ZAP-70 is recruited, resulting in a series of phosphorylation events (Smith-Garvin et al., 2009).

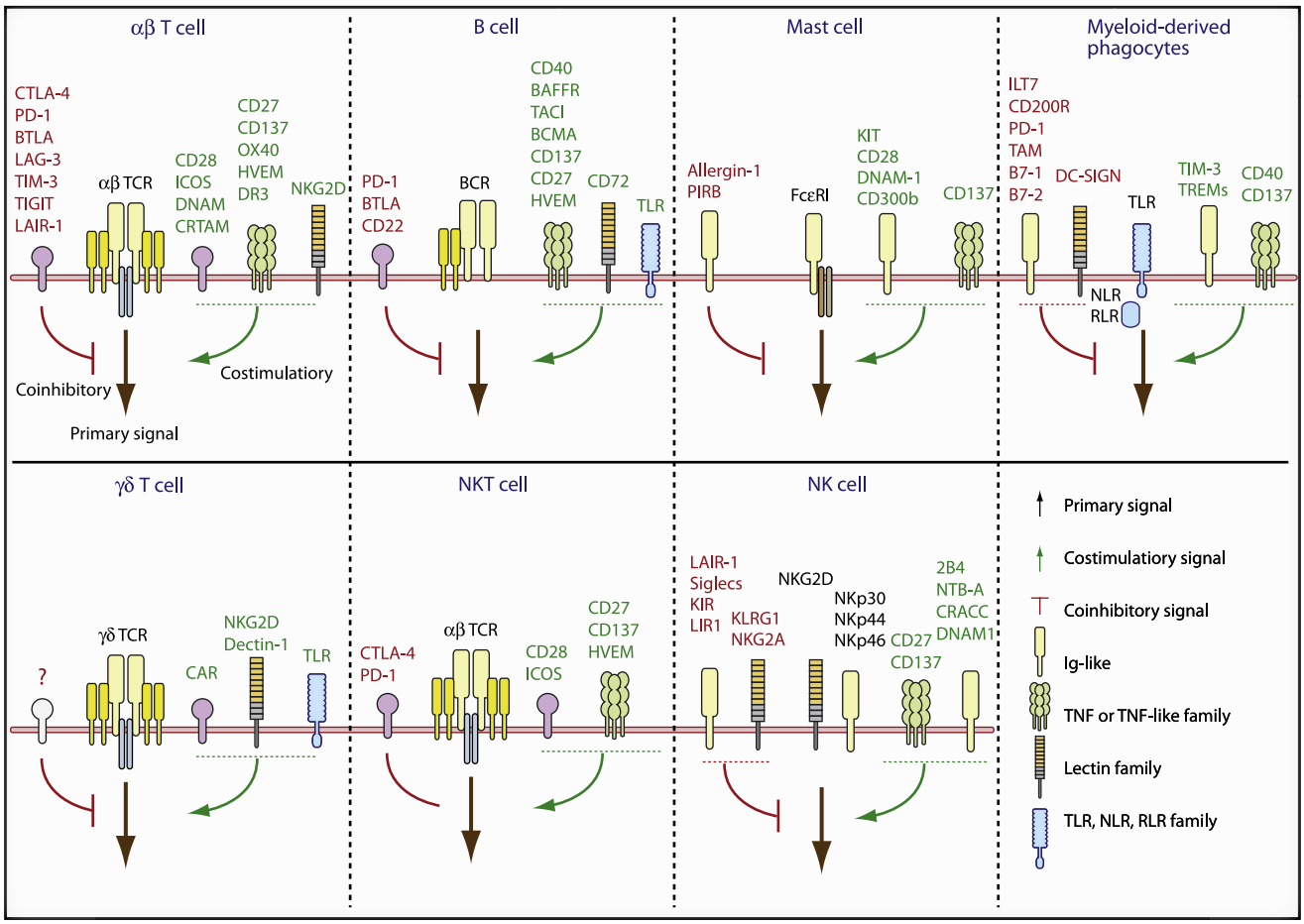

Figure 2. Cell Surface Signaling Molecules in the Control of Immune Responses
The major primary signal and cosignal (costimulatory or coinhibitory) molecules are shown in each immune cell type. TLR, Toll-Like Receptor; RLR, RIG-like Receptors; NLR, NOD-like Receptor.

The majority of cosignaling molecules for conventional T cells stem from the B7 family and TNF superfamily of receptors (Table 1). In addition to interactions between CD28 and CTLA-4 receptors with their ligand B7-1 (CD80) and B7-2 (B70, CD86) (Greenwald et al., 2005), several recent studies add new perspectives for this classic pathway. B7-1 has been found to interact with B7-H1. In this case, B7-1 serves as a receptor to inhibit T cell responses in vitro (Butte et al., 2007) and contributes to the induction of T cell tolerance in vivo (Park et al., 2010). B7-H2, a molecule best known as the ligand for Inducible Costimulator (ICOS), is found to be a costimulatory ligand for CD28 in vitro (Yao et al., 2011). Interestingly, this interaction is only found in human, not in mouse, warranting re-evaluation of data previously obtained from mouse models. Herpesvirus entry mediator (HVEM), a member of the TNF receptor (TNFR) superfamily, is commonly recognized as a costimulatory receptor for LIGHT (TNFSF14) and lymphotoxin- α (Xu et al., 2007). Interestingly, HVEM has recently been found to interact with B and T lymphocyte attenuator (BTLA) and CD160, and deliver a suppressive signal to T cells (Cai et al., 2008; Watanabe et al., 2003). The complex molecular network between HVEM and its binding partners makes bidirectional signaling feasible and reveals surprising cross-talk between TNFR superfamilies and Ig-like receptors. In addition to the B7 and TNF families, several new families of molecules have emerged with potent cosignaling function, including T cell immunoglobulin domain and mucin domain (TIM) family, poliovirus receptor (PVR)-like proteins (Bottino et al., 2003; Xu and Jin, 2010; Yu et al., 2009), semaphorins (Kumanogoh et al., 2002; Takegahara et al., 2006; Wen et al., 2010), and butyrophilin-like molecules (Nguyen et al., 2006; Smith et al., 2010; Stefferl et al., 2000).

Why do T cells need so many cosignals? One simple answer for this question is that T cell activation is an instructively programmed process and every step of a T cell response is tightly controlled by many different groups of cosignaling molecules with both costimulatory and coinhibitory functions. A typical T cell response evolves at least three steps: priming, expansion, and contraction. Costimulators, such as CD27, CD28, and HVEM, which are constantly expressed on naive T cells, are known to be important initiators for naive T cell activation in lymphoid organs in the presence of a TCR signal (Sharpe, 2009; Watts, 2005), while the majority of coinhibitory receptors are undetectable during this period. Further expansion of such T cells requires signals through ICOS, death receptor 3 (DR3),

CD137, and OX40 (Sharpe, 2009; Watts, 2005). If coinhibitory ligands are available in lymphoid organs, coinhibitory molecules like CTLA-4, PD-1, BTLA, and LAG-3 are now unregulated and make activated T cells susceptible to negative control (Chen, 2004; Murphy et al., 2006; Okazaki et al., 2011). This could be considered the first level of negative control. For example, expression of B7-H1 is found to be upregulated in lymph nodes, upon interacting with PD-1, leading to tolerance induction of T cells (Tsushima et al., 2007). Upon exit from lymphoid organs and arrival into the periphery, effector T cells begin to execute their functions. OX40 and CD137 have proven to be critical for effector T cell survival and therefore memory T cell generation (Watts, 2005). During and after execution of effector functions, effector T cells are subjected to another level, and possibly the most severe negative regulation. Peripheral organs and tissues are equipped with various coinhibitory ligands including B7-H1, B7-H4, Galectin-9, PVR, Semaphorins, V-set, and immunoglobulin domain containing 4 (VSIG4) (Vogt et al., 2006) and butylophines, which are ready to either tune down or terminate effector T cells. Therefore, different cosignaling molecules may form distinct groups to regulate various stages of T cell activation.

Diverse expression of cosignaling molecules also allows differential control of T cell subsets and their "personalized" characters are critical to modulating immune responses. For example, CD137 is a potent costimulator for $CD8^+$ T cells, while its effects on $CD4^+$ T cell are less profound (Watts, 2005). On the contrary, OX40 and ICOS are found to preferentially costimulate $CD4^+$ over $CD8^+$ T cells despite the fact that they are induced on both activated $CD4^+$ and $CD8^+$ T cells (Greenwald et al., 2005; Watts, 2005). These results suggest an intrinsic difference between $CD4^+$ and $CD8^+$ T cells in responding to cosignals. Another example is that, although both CTLA-4 and PD-1 are coinhibitory for effector T cells, blockage of PD-1 signal, but not CTLA-4, restores the function of exhausted T cells, thereby reducing viral load during chronic viral infection (Barber et al., 2006). This would support the concept that PD-1 selectively controls the exhaustion phenotype. In many cases, distinct expression patterns of cosignaling molecules have selective effects on T cell subsets. Both B7-DC and B7-H1 deliver an inhibitory signal to T cells through their shared receptor PD-1 (Chen, 2004). The expression of B7-DC is restricted to professional APCs such as DCs. In contrast, B7-H1 mRNA is present in almost all peripheral tissues and cell surface protein expression is extremely sensitive to the regulation by proinflammatory cytokines (Chen, 2004). As a result, the role of B7-DC is limited to T cell priming, while the role of B7-H1 on T cells could be broad: acting on both priming and effector phases.

CD28 is constitutively present on T cells, providing instant help to potential T cell activation. Meanwhile, its counterpart, CTLA-4, is mainly found in intracellular reservoirs, which allows CTLA-4 to rapidly transport to the cell surface in response to antigenic stimuli and to exert its immune-modulatory function (Schneider et al., 2006). Interestingly, CTLA-4 is constitutively present on the surface of fox-head box protein 3 $(Foxp3)^+$ regulatory T (T_{reg}) cells and is required for the maintenance of T_{reg} cell function in vivo (Wing et al., 2008). Meanwhile the coinhibitory PD-1 protein is not expressed on naive T cells yet is transiently induced on activated T cells (Chen, 2004). However, PD-1 is highly expressed on T cells with exhausted phenotypes, induced by constant exposure to antigen stimuli during chronic viral infection or malignancy. Blockade of the PD-1 pathway restores T cell function, emphasizing the critical role of PD-1 in T cell dysfunction during chronic viral infection (Barber et al., 2006). Thus, the expression pattern of each cosignaling molecule contributes greatly to their differential regulatory functions.

Our understanding of how intracellular biochemical pathways transmit cosignals is still rudimentary. This is largely due to an absolute dependence of cosignal function on TCR-mediated signaling. Given the overlapping but distinctive function of cosignals, it is not difficult to understand that cosignaling molecules regulate T cell immunity utilizing both shared and unique signaling pathways. The most straightforward strategy is to consider intracellular motifs from each cosignaling receptor. One common pathway for CD28 and its family members, such as ICOS and CTLA-4, is the recruitment of class 1A forms of phosphatidylinositol 3-kinase (PI3K) to their cytoplasmic domains (Rudd and Schneider, 2003). Unlike CD28, ICOS lacks the intracellular motif to bind growth-factor receptor-bound protein 2 (GRB2), which might contribute to its ineffective induction of IL-2 production (Rudd and Schneider, 2003). Coinhibitory receptors such as PD-1 and BTLA utilize the immunoreceptor tyrosine-based inhibitory motif (ITIM) to recruit SRC homology 2 (SH2)-domain-containing protein tyrosine phosphatase 2 (SHP-2) or SHP-1 and SHP-2, which dephosphorylates and therefore deactivates downstream signal transducers (Greenwald et al., 2005; Watanabe et al., 2003). Cosignaling receptors from the TNFR superfamily contain the intracellular regions necessary for interacting with TNFR-associated factors (TRAFs) (Croft, 2009). TRAFs can recruit inhibitors of nuclear factor-κB (NF-κB), α subunit (IκBα), IκB kinase-β (IKKβ), and NF-κB-inducing kinase (NIK), leading to the activation of both canonical and noncanonical NF-κB pathways that are essential for cell survival (Vallabhapurapu and Karin, 2009). Several TNFR coreceptors also activate signaling pathways other than NF-κB, which might not be shared among TNFR members but contribute to their regulatory functions. For instance, ligation of CD137 activates extracellular-signal-regulated kinase (ERK) and regulates the expression of cyclins (Watts, 2005). Meanwhile, signaling through the TNFR OX40 promotes the expression of survivin and aurora B kinase (Sugamura et al., 2004).

There are numerous studies detailing the coordination of cosignals with TCR signals (Sharpe, 2009; Smith-Garvin et al., 2009). Engagement of TCR regulates the expression of several cosignaling molecules on T cells, and the strength of Signal 1 presumably affects the recruitment of cosignaling molecules to the immune synapse (Egen and Allison, 2002). TCR ligation alone can trigger many signaling pathways; however, the magnitude of the response is considerably altered in the presence of cosignaling molecules. It appears that engagement of cosignaling molecules results primarily in a quantitative, rather than a qualitative, change in T cell signaling parameters (Smith-Garvin et al., 2009).

γδ T Lymphocytes

γδ T cells represent a small subset of T cells that possess a unique TCR and preferentially reside within epithelial-rich tissues, such as the skin, intestine, and reproductive tracts. γδ T cells recognize conserved nonpeptide antigens that are upregulated by stressed cells in an MHC-independent manner. The physiological roles of γδ T cells include protective immunity

Table 1. Signal 1 and Cosignals for Immune Cell Subsets

Cell type	Signal 1	Cosignals	Receptor	Ligand(s)	Intracellular Signaling	Reference(s)
T cell (αβ)						
	TCR	Costimulator	CD28	B7-1, B7-2, B7-H2 (h)*	PI3K, GRB2, Vav	(Rudd and Schneider, 2003)
			ICOS	B7-H2	PI3K	(Rudd and Schneider, 2003)
			TLT2?	B7-H3	-	(Hashiguchi et al., 2008; Leitner et al., 2009)
			-	B7-H1, B7-DC	-	(Wang et al., 2003)
			CD27	CD70	NF-kB, Bcl2	(Watts, 2005)
			CD137	CD137L	NF-kB, Bcl-2,Erk	(Watts, 2005)
			OX40	OX40L	NF-kB, Bcl-2, PI3K	(Watts, 2005)
					Survivin	(Watts, 2005)
			HVEM	LIGHT	NF-kB	(Mauri et al., 1998)
			DR3	TL1A	NF-kB	(Migone et al., 2002)
			NKG2D	MICA, MICB	DAP-10	(Moretta et al., 2001)
				ULBP-4, RAET1G		(Moretta et al., 2001)
			TIM-1	TIM-4, phosphatidylserine	-	(Meyers et al., 2005; Miyanishi et al., 2007)
			TIM-2	H-Ferritin, Sema4A?	-	(Chen et al., 2005; Kumanogoh et al., 2002)
			DNAM-1	PVR, PVRL2	-	(Bottino et al., 2003)
			CRTAM	Necl2	Scrib	(Takeuchi et al., 2009)
		Coinhibitor	CTLA-4	B7-1, B7-2, B7-H2 (h)*	PI3K, SHP-2, PP2A	(Rudd and Schneider, 2003)
			PD-1	B7-H1, B7-DC	SHP-2	(Fife et al., 2009)
			B7-1	B7-H1	-	(Butte et al., 2007; Park et al., 2010)
			-	B7-H3	-	(Chapoval et al., 2001)
			-	B7-H4	-	(Sica et al., 2003)
			BTLA	HVEM	SHP-1, SHP-2	(Watanabe et al., 2003)
			CD160	HVEM	-	(Cai et al., 2008)
			LAG-3	MHC II	-	(Huard et al., 1994)
			TIM-3	Galectin-9, phosphatidylserine	Ca^{2+}	(Nakayama et al., 2009; Zhu et al., 2005)
			TIGIT	PVR, PVRL2, PVRL3	-	(Yu et al., 2009)
			LAIR-1	Collagen	SHP-1, SHP-2	(Lebbink et al., 2006)
			-	VSIG4	-	(Vogt et al., 2006)
			-	Sema3A	-	(Wen et al., 2010)
			-	BTNL1	-	(Bas et al., 2011)
			-	BTNL2	-	(Nguyen et al., 2006)
			-	BTN1A1	-	(Smith et al., 2010)
			-	BTN2A2	-	(Smith et al., 2010)
T cell (γδ)						
	TCR	Costimulator	NKG2D	MICA, MICB	DAP-10	(Whang et al., 2009)
			CAR	JAML	PI3K	(Verdino et al., 2010; Witherden et al., 2010)
			CD137	CD137L	NF-kB, Bcl-2,Erk	(Zhou et al., 1994)
NKT						
	iTCR	Costimulator	CD28	B7-1, B7-2	PI3K, GRB2, Vav	(van den Heuvel et al., 2011)
			ICOS	B7-H2	PI3K	(van den Heuvel et al., 2011)
			CD40	CD40L	TRAF2, 5, 6, JNK, p38	(van den Heuvel et al., 2011)
			OX40	OX40L	NF-kB, Bcl-2, PI3K	(van den Heuvel et al., 2011)
			CD137	CD137L	NF-kB, Bcl-2,Erk	(van den Heuvel et al., 2011)
			TIM-1	TIM-4, phosphatidylserine	-	(van den Heuvel et al., 2011)

Table 1. *Continued*

Cell type	Signal 1	Cosignals	Receptor	Ligand(s)	Intracellular Signaling	Reference(s)
		Coinhibitor	PD-1	B7-H1, B7-DC	SHP-2	(van den Heuvel et al., 2011)
			BTLA	HVEM	SHP-1, SHP-2	(van den Heuvel et al., 2011)
			GITR	GITRL	-	(van den Heuvel et al., 2011)
B Cell						
	BCR	Costimulator	CD40	CD40L, C4BP	TRAF2, 5, 6, JNK, p38	(Grewal and Flavell, 1998)
			HVEM	LIGHT	NF-kB?	(Duhen et al., 2004)
			CD137	CD137L	NF-kB?	(Zhang et al., 2010)
			CD27	CD70	NF-kB	(Kobata et al., 1995)
			BAFF-R	BAFF	NF-kB2, PI3K-Akt1-mTOR	(Mackay and Schneider, 2009)
			TACI	BAFF, APRIL	NF-kB1, MyD88	(Mackay and Schneider, 2009)
			BCMA	BAFF, APRIL	NF-kB	(Mackay and Schneider, 2009)
			CD72	CD100	Grb2/CD19-PI3K	(Kumanogoh et al., 2000)
		Coinhibitor	PD-1	B7-H1, B7-DC	SHP-2	(Good-Jacobson et al., 2010; Okazaki et al., 2001)
			BTLA	HVEM	SHP-1	(Vendel et al., 2009)
			CD72	CD100	SHP-1	(Kumanogoh et al., 2000)
			CD22	Sialic acid	SHP-1	(Kawasaki et al., 2010)
NK Cell						
	NKG2D	Costimulator	DNAM-1	PVRL2, PVR	-	(Tahara-Hanaoka et al., 2004)
	NKp30		CD96	PVR	-	(Xu and Jin, 2010)
	NKp44		CD137	CD137L	-	(Wilcox et al., 2002)
	NKp46		CD27	CD70	-	(Takeda et al., 2000)
			2B4	CD48	SAP	(Vivier et al., 2011)
			NTB-A	NTB-A	SAP	(Vivier et al., 2011)
			CRACC	CRACC	SAP/EAT-2	(Vivier et al., 2011)
		Coinhibitor	LAIR-1	Collagen	SHP-1, 2	(Lebbink et al., 2006)
			Siglec-3.7.9	Sialic acid	SHP-1, 2	(Avril et al., 2004; Hernández-Caselles et al., 2006)
			PD-1	B7-H1, B7-DC	SHP-2	(Alvarez et al., 2010)
			KLRG1	Cadherins	SHP-1, 2	(Vivier et al., 2011)
			NKR-P1A	CLEC2D	SHP-1, 2	(Vivier et al., 2011)
			ILT2	HLA class I	SHP-1, 2	(Vivier et al., 2011)
			KIR2DL1,2,3	HLA-C	SHP-1, 2	(Vivier et al., 2011)
			KIR3DL1,2	HLA-A/B	SHP-1, 2	(Vivier et al., 2011)
			CD94-NKG2A	HLA-E	SHP-1, 2	(Vivier et al., 2011)
			2B4	CD48	EAT-2, Csk	(Moretta et al., 2001)
Myeloid Cells (DCs, Macrophages, Monocytes)						
	TLR	Costimulator	B7-1, B7-2	CD28	p38, MAPK	(Orabona et al., 2004)
	RLR		Plexin-A1	Sema6D	TREM2-DAP12	(Takegahara et al., 2006)
	NLR		Plexin-A4	Sema3A	Rac1	(Wen et al., 2010)
			CD137	CD137L	Stat 3	(Vinay and Kwon, 2011)
			CD40	CD40L	NF-kB	(Kikuchi et al., 2000)
			CD300b,e	-	DAP12, Grb2	(Clark et al., 2009)
			TREM1,2,3	-	DAP12	(Ford and McVicar, 2009)
		Coinhibitor	ILT7	BST2	FcεRIγ	(Brown et al., 2004)

(*Continued on next page*)

Table 1. *Continued*

Cell type	Signal 1	Cosignals	Receptor	Ligand(s)	Intracellular Signaling	Reference(s)
			ILT3,4	-	SHP-1,2	(Brown et al., 2004)
			TLT-1	-	SHP-1,2	(Ford and McVicar, 2009)
			CD200R	CD200	Dok1, Dok2	(Hoek et al., 2000)
			PD-1	B7-H1, B7-DC	JNK, PI3K	(Said et al., 2010)
			TAM family	GAS6/protein S	SOCS1, SOCS3	(O'Neill, 2007)
			CD300a,f	-	SHP-1,2	(Clark et al., 2009)
			DC-SIGN	Carbohydrate	Raf-1	(Gringhuis et al., 2007)
			B7-1, B7-2	CTLA-4	Stat1, p38, MAPK	(Grohmann et al., 2002)
Mast Cell						
	FcεRI	Costimulator	Kit	SCF	SHC, Grb2, PI3K, PLCγ	(Sayed et al., 2008)
			CD137	CD137L	Lyn	(Sayed et al., 2008)
			CD28	B7-1, B7-2	Syk	(Sayed et al., 2008)
			DNAM-1	PVR, PVRL2	Fyn, LAT, PLCγ2	(Sayed et al., 2008)
			CD300b	TIM-1	DAP12	(Yamanishi et al., 2010)
		Coinhibitor	Allergin-1	-	SHP-1,2	(Hitomi et al., 2010)
			Pir-B	MHC class I	SHP-1.2	(Uehara et al., 2001)
			Gp49B1	-	SHP-1,2	(Sayed et al., 2008)
			CD300a	-	SHP-1,2	(Bachelet et al., 2005)

"-" indicates that it is unknown. "*" indicates that the interaction is human-specific. "?" indicates that the interaction is controversial.

against pathogens, tumor surveillance, and wound healing (Bonneville et al., 2010). γδ T cells do not express CD28 or ICOS, and the role of cosignaling in γδ T cell activation has only recently been investigated. NKG2D, which is known to costimulate $CD8^+$ αβ T cell, promotes the cytotoxicity and IL-2 secretion of γδ T cells (Whang et al., 2009). Another important cosignaling pathway for γδ T cells is the junctional adhesion molecule-like protein (JAML)-coxsackie and adenovirus receptor (CAR) pair (Verdino et al., 2010; Witherden et al., 2010). The JAML protein is selectively expressed on γδ T cell, but not on αβ T cells. Signaling through JAML costimulates γδ T cell proliferation and cytokine production, presumably through recruitment and activation of PI3K (Verdino et al., 2010). In vivo blockade of JAML-CAR interaction results in diminished γδ T cell activation and therefore delayed wound healing (Witherden et al., 2010).

B Lymphocytes

B lymphocytes are the central mediators of humoral responses. The generation of plasma cells and long-lived memory B cells is a tightly regulated process, which involves an ordered series of molecular and cellular changes in vivo. Upon encountering antigen, B cells rapidly proliferate and undergo class switching and somatic hypermutation (McHeyzer-Williams and McHeyzer-Williams, 2005). This process usually happens in the germinal centers and requires cellular coordinative interactions among follicular DCs, helper T cells, and B cells (McHeyzer-Williams and McHeyzer-Williams, 2005). In addition to cytokines, CSSMs are known to be critical for B cell activation, as originally proposed in the two-signal model (Bretscher and Cohn, 1970).

The primary signal for B cells is mediated through the B cell receptor (BCR), which is a multiprotein complex containing a membrane-bound Ig for antigen-binding and two noncovalently associating elements (Ig-α and Igβ) for signal transduction (Kurosaki et al., 2010). Upon antigen binding, BCR signals are initiated by SRC family kinases, like Lyn, which phosphorylate ITAMs on the BCR complex, thereafter recruiting and phosphrylating Syk (spleen tyrosine kinase). Subsequently, a series of signaling cascades are triggered, which include the PI3K pathway, the activation of phospholipase-C γ2 (PLCγ2), and the increase of intracellular calcium, all of which change cellular metabolism, gene expression, and cytoskeleton organization. However, the complexity of BCR signaling itself permits many distinct outcomes, which include anergy, apoptosis, proliferation, and differentiation into plasma cells or memory B cells (Kurosaki et al., 2010). Similar to T cells, the ultimate outcome of the response is largely controlled by signals from CSSMs.

Currently, members of the TNFR superfamily are dominant in delivering costimulatory signals to B cells. Among them, many costimulatory pathways also provide cosignal for T cells, including CD27-CD70, CD137-CD137L, and HVEM-LIGHT interactions (Duhen et al., 2004; Kobata et al., 1995; Zhang et al., 2010). The CD40-CD40L pair is the best-studied pathway and plays an indispensable role in T cell-dependent B cell responses (Grewal and Flavell, 1998). CD40 ligation stimulates B cell proliferation, survival, isotype switching, formation of the germinal center (GC), and memory B cell generation. Mice deficient in CD40L or CD40 are unable to generate a primary or a secondary antibody response to a T cell-dependent antigen; do not form GCs; and are deficient in generating antigen-specific memory B cells (Grewal and Flavell, 1998). CD40 signaling in B cells leads to the recruitment of TRAFs, thereafter leading to the activation of NF-κB and the MAP kinases JNK and p38. BAFF (B cell activating factor belonging to the TNF family), together with its close homolog APRIL (a proliferation inducing ligand), are key regulators for B cell homeostasis (Mackay and Schneider, 2009). In addition to their crucial roles in B cell development

and survival, they are also essential for peripheral B cell activation. BAFF and APRIL both bind to TACI (transmembrane activator and CAML interactor) and BCMA (B cell maturation protein A), and BAFF also interacts with BAFF receptor (BAFFR). BAFF interacts with BAFFR to control the development and survival of B2 cells and marginal zone B cells (Mackay and Schneider, 2009). APRIL binds to TACI to accelerate CD40-independent class switching (Mackay and Schneider, 2008), while also promoting plasma cell survival through the BCMA receptor (O'Connor et al., 2004). As members of the TNFR superfamily, stimulation of BAFFR, TACI, and BCMA receptors triggers the recruitment of TRAF adaptor proteins to activate NF-κB pathways, which are critical for B cell survival. Signaling through BAFFR preferentially activates the alternative NF-κB2 pathway, whereas TACI is a potent stimulator of the classical NF-κB1 pathway. BCR signaling is required to provide substrates for sustaining the NF-κB2 pathway triggered by BAFF. In addition, BAFFR signals can activate the PI3K-AKT1-mTOR pathway to promote cellular metabolism (Mackay and Schneider, 2009). In addition, TACI triggers class switching through direct associating with the adaptor MyD88 (He et al., 2010). Similar to T lymphocytes, B cells express several coinhibitory receptors. PD-1, now known as a key T cell checkpoint modulator, was originally thought of as a coinhibitor for B cells (Okazaki et al., 2001). Ligation of the PD-1 intracellular domain recruits the phosphatase SHP-2, leading to the inhibition of BCR signaling by dephosphorylating several key signal transducers in vitro (Okazaki et al., 2001). Several recent studies support PD-1 as a regulator for GC B cell survival and formation of memory plasma cells because PD-1 deficiency or deficiency of its ligand B7-H1 and B7-DC results in impaired memory B cell pools, likely mediated by poor survival of follicular helper T cells (Good-Jacobson et al., 2010). Similarly BTLA, another T cell coinhibitor, attenuates BCR signaling by recruiting SHP-1 (Vendel et al., 2009).

Natural Killer Cells

Natural killer (NK) cells are cytotoxic lymphocytes that mediate innate immunity against viral infection and tumors. A major difference of NK cells from other lymphocyte lineages is that they often utilize multiple activating receptors to transmit primary signals, leading to rapid activation of NK cells (Moretta et al., 2001). This is understandable in the context of NK cell functions as the host's rapid reacting force to survey the tissues for abnormality. Functions of these germline-encoded receptors, however, are still tightly regulated by a great number of cell surface cosignaling molecules. The activation of NK cells can result in direct cytotoxic attack on their targets and/or secretion of array of cytokines and chemokines, which contributes to initiation of antigen-specific responses. NK cells are also armed with a large number of coinhibitory molecules that control their activity.

NK cell use multiple surface receptors to distinguish normal healthy cells with abnormal cells undergoing various forms of stress, such as viral infection or tumor transformation. Some receptors detect viral proteins on the surface of infected cells, which are structurally similar to MHC and otherwise intend to evade immune recognition (Natarajan et al., 2002). Some receptors can identify a type of stress molecule expressed on the surface of viral-infected or malignant-transformed cells. Those stress molecules are encoded by the host's genome, yet are rarely expressed by normal cells but upregulated by stressed or diseased cells. For example, NKG2D identifies a series of MHC-like ligands preferentially present on many tumor cells (Raulet, 2003). In addition to its ability to bind to cytomegalovirus (CMV) pp65, NKp30 has recently been shown to be a receptor for B7-H6, a protein not found on normal cells but highly expressed on varieties types of tumor cell lines (Brandt et al., 2009). These activating NK cell receptors often have short intracellular domains that lack intrinsic signaling activity. Their charged transmembrane regions, however, can associate with transmembrane adaptor molecules to transmit signals. For instance, NKp44 couples to DAP12 while NKG2D uses the adaptor protein DAP10 (Moretta et al., 2001). CD16, NKp30, and NKp46 receptors associate with FcεRIγ and CD3ξ (Vivier et al., 2004).

Since NK cells share a common progenitor with T cells and in many aspects are very closely related to T cells, it is not surprising that a lot of surface molecules are shared between NK cells and T cells. Many cosignaling molecules for T cells, like CD137 (Wilcox et al., 2002), CD27 (Takeda et al., 2000), CD96 (Fuchs et al., 2004), DNAM-1 (CD226) (Tahara-Hanaoka et al., 2004), and LAIR-1 (Meyaard et al., 1997), are also found to be crucial for NK cell activation, though their exact roles in two cell types might not be identical. Signaling lymphocytic activation molecule (SLAM)-related and PVR-like proteins are two main families that are important for the regulation of NK cell function. SLAM family proteins have been shown to exhibit homotypic interactions with the exception of 2B4, which recognizes CD48. Interestingly, 2B4 can act as both a costimulatory receptor and coinhibitory receptor for NK cells depending on the signaling pathways it initiates (Moretta et al., 2001). The positive role of 2B4 requires its association with SLAM-associated protein (SAP), leading to activation of numerous intracellular molecules, such as Vav-1, PLCγ, and SHIP (Cannons et al., 2011). In the absence of SAP, 2B4 may deliver a negative signal to NK cells by recruitment of EAT-2 or Csk. CD96 (Tactile) and DNAM-1 are two receptors for PVR-like family ligands and promote adhesion to ligand-expressing targets and enhance the cytolytic capability of NK cells (Xu and Jin, 2010). In contrast, engagement of TIGIT on NK cells by PVR leads to an ITIM-mediated suppression (Stanietsky et al., 2009). One common feature for NK cell coinhibitory receptors is that they contain an intracellular ITIM motif. Many coinhibitory receptors for NK cells, such as CD94-NKG2A, KIR2DL1-3, and KIR3DL1-2, recognize MHC molecules, which allow normal cells to avoid NK cell killing (Lanier, 2005). Other important coinhibitory pathways include LAIR-1-collagen, NKR-P1A-CLEC2D, KLRG1-cadherins (Vivier et al., 2011), and ITIM-containing SIGLEC family members (SIGLEC3, SIGLEC7, and SIGLEC9), which recognize sialic acid-containing molecules (Avril et al., 2004; Hernández-Caselles et al., 2006).

Myeloid-Derived Phagocytes

Monocytes and macrophages and dendritic cells represent two subgroups of the mononuclear phagocyte system originally described as a population of bone marrow-derived myeloid cells (van Furth and Cohn, 1968). Monocytes are those circulating in the blood while macrophages reside in tissues in the steady state as well as during inflammation. Monocytes and macrophages are critical effectors and regulators of inflammation (Dale et al.,

2008). Dendritic cells specialize in initiating and regulating pathogen-specific adaptive immunity and are central to the development of adaptive immune response (Mellman and Steinman, 2001). A series of pattern recognition receptors (PRRs) are utilized to receive primary signal to execute their distinctive functions, including inflammation, opsonization, activation of complement and coagulation cascades, and phagocytosis (Janeway and Medzhitov, 2002). These PRRs can be expressed on the cell surface, expressed in intracellular compartments, or secreted into the bloodstream. Several classes of PRRs involved in different aspects of immune functions for those myeloid cells have been illustrated recently (Palm and Medzhitov, 2009). Here we will focus on the inflammatory response as an example to discuss the decision-making process for these myeloid cells—that is, how inflammation is regulated by cosignals.

Pathogen infection is the most common way of triggering an inflammatory response, as phagocytes express PRRs to recognize molecular motifs conserved within a class of microbes, which are often named as pathogen-associated molecular patterns (PAMPs) (Janeway, 1989). These receptors can be considered to transduce a primary signal. Recent studies indicate that PRRs are also responsible for recognizing endogenous molecules released from damaged cells, termed damage-associated molecular patterns (DAMPs) (Seong and Matzinger, 2004). Currently, at least three types of PRR families have been identified (Takeuchi and Akira, 2010). These families include the Toll-like receptors (TLRs), the Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs). TLRs, including ten functional members in human, are the first and best characterized PRR family that sense invading pathogens outside of the cell as well as in intracellular endosomes and lysosomes. Both RLRs and NLRs families are cytoplasmic proteins, with RLRs recognizing short double-stranded RNA derived from viruses while NLRs sensing DAMPs caused by tissue injury (Bowie and Unterholzner, 2008; Philpott and Girardin, 2010).

The activation of these PRRs involves distinctive signaling cascades, leading to the secretion of different patterns of proinflammatory cytokines. TLR activation leads to the direct interactions of the Toll-IL-1 receptor (TIR) domain with a cytoplasmic TIR-containing adaptive molecule, such as MyD88 or TRIF (Takeda and Akira, 2004). Activation of the MyD88-dependent signaling pathway results in the activation of the classic NF-κB pathway, which leads to the expression of numerous proinflammatory cytokines, such as IL-6, IL-12, and TNF-α. TRIF is required for the MyD88-independent pathway in TLR3- and TLR4-mediated responses. The recruitment of TRIF leads to the activation of transcription factor IRF-3, thereby inducing type I interferon (IFN) secretion. The RLR family has at least three members: RIG-I, MDA5, and LGP2 (Nakhaei et al., 2009). They are composed of two N-terminal caspase recruitment domains (CARDs), a central DEAD box helicase domain, and a C-terminal regulatory domain. RLRs recognize dsRNA from RNA viruses in cytoplasm. Activation of RIG-I and MDA5 leads to its homophilic interaction with IPS-1 through CARD domains, turning on signaling cascades resulting into the expression of type I IFN genes. The NLR family contains more than twenty members in human and their domain architecture consists of a variable N-terminal effector domain, a central nucleotide-binding domain (NBD) and C-terminal leucine-rich repeats (LRRs) (Philpott and Girardin, 2010). NOD2 senses bacterial infection and interacts with the receptor-interacting serine-threonine protein kinase 2 (RIPK2) to activate NF-κB and MAPK, therefore promoting the expression of proinflammatory molecules (Strober et al., 2006). The NLR family members NLRP1, NLRP3, and NLRC4 assemble large protein complexes known as inflammasomes, which respond to DAMPs and are responsible for the activation of caspase-1 and hence the production of IL-1β and IL-18 (Philpott and Girardin, 2010).

Unlike T cells, the innate immune response mediated by DCs, monocytes, and macrophages is a rapid process and does not require any antigen processing. Yet unrestrained signaling by PRRs in DCs and macrophages would generate a chronic inflammatory milieu or cytokine storm that can lead to sepsis. As for any dynamic system, the innate immune response must be carefully regulated so that turning it on must be followed with a mechanism that can turn it off. In fact, many coreceptors on these myeloid cells function as pivotal regulators that can either positively or negatively control inflammation, which here we call as cosignals. Similar to T cell cosignals, cosignaling molecules for DCs, macrophages, and monocytes belong to many molecular families, and many of them have preferential roles on these cell types. For example, CD200R, a member of the Ig superfamily, is a coinhibitory receptor mainly on tissue macrophages (Hoek et al., 2000). In contrast, DC-SIGN is a C-type lectin molecule preferentially found on DCs (Geijtenbeek et al., 2000).

Each cosignal utilizes different intracellular machinery to modulate TLR signaling. Many members of the triggering receptor expressed on myeloid cells (TREM) family modulate myeloid cell function through their association with DAP12 (Ford and McVicar, 2009). Another costimulatory pathway for myeloid cells is the plexin-A4-Sema3A pair (Wen et al., 2010). Plexin-A4 genetically targeted mice are highly resistant to septic shock induced by TLR agonists, and its ligand, Sema3A, promotes LPS-induced cytokine production through plexin-A4. Signaling studies indicate that Plexin-A4 is required for TLR-induced activation of Ras-related C3 botulinum toxin substrate 1(Rac1), c-Jun N-terminal kinase (JNK), and NF-κB. In contrast, Sema6D-plexin-A1, another pair belonging to the plexin-semaphorin family, induces DCs maturation through a different pathway (Takegahara et al., 2006). Sema6D promotes the association between plexin-A1 and Trem-2, therefore recruiting adaptor DAP12 to activate downstream signaling.

One common pathway for coinhibitory molecules to dampen TLR-mediated inflammatory pathways in myeloid cells is through the ITIM motif within the cytoplasmic domain that is used to recruit and interact with the phosphatases SHP-1 and SHP-2. Those proteins are mainly Ig superfamily members, including inhibitory members of Ig-like transcripts (ILTs), CD300 family (Clark et al., 2009), and TREM-like transcript-1 (TLT-1) (Ford and McVicar, 2009). CD200R does not have an ITIM but instead contains an NPxY motif in its cytoplasmic domain to recruit inhibitory adaptor proteins Dok1 and Dok2 (Minas and Liversidge, 2006). Another good example of coinhibitory molecules for DCs is DC-SIGN, which recognizes the carbohydrate motifs on its ligands to tailor TLR signaling on DCs. DC-SIGN engagement modifies TLR signaling by activating the serine-threonine kinase Raf-1, leading to acetylation of the p65 subunit of NF-κB (Gringhuis et al., 2007).

Mast Cells

The mast cell is a major cell type playing a key role in allergic inflammatory responses. Mast cells bind to aggregated IgE induced by allergen and rapidly release numerous proinflammatory mediators, a process referred as degranulation. In the past decade mast cells have been recognized as immune cells that not only act as key effector cells in allergic responses, but also execute regulatory functions in innate as well as adaptive immune responses (Sayed et al., 2008).

The primary signal to initiate mast cell activation is triggered by allergen-induced aggregation of high-affinity receptors for IgE (FcεRIs) (Sayed et al., 2008). The FcεRI receptor is a tetrameric complex that comprises an α chain, which is responsible for IgE binding, a β-chain, and a disulphide-linked γ-chain homodimer, which are responsible for signaling. Following FcεRI aggregation, the protein tyrosine kinases FYN and Syk become activated, which results in tyrosine phosphorylation of the adaptor molecule GAB2 and subsequently the activation of phosphatidylinositol 3-kinase (PI3K) and PLCγ (Sayed et al., 2008). The transmembrane adaptor molecules LAT and NTAL are crucial for coordination of the downstream signaling pathways that are required for the release of the various proinflammatory mediators.

CD28, DNAM-1, and CD137 are T cell costimulatory receptors known to regulate mast cell function as well (Sayed et al., 2008). SCF-KIT is the most well-studied costimulatory pathway for mast cells (Sayed et al., 2008). SCF alone does not induce mast cell degranulation while simultaneous addition of SCF and antigen markedly increases the secretion of multiple cytokines in both human and mouse mast cells. SCF signaling results in the activation numerous signaling pathways, including the activation of PI3K, PLCγ, calcium mobilization, and MAPK-cascade, which are also triggered by FcεRI stimulation. However, SCF stimulation fails to induce tyrosine phosphorylation or to activate PKC, which might explain its inability to stimulate mast cell degranulation by itself (Sayed et al., 2008). The coinhibitory receptors for mast cell include PIR-B (Uehara et al., 2001), CD300a (Bachelet et al., 2005), gp49B1 (Sayed et al., 2008), and allergin-1 (Hitomi et al., 2010), which all contain ITIMs within their cytoplasmic domains. During the initiation of mast cell activation, the phosphorylation of ITIMs recruits the tyrosine phosphatases SHP-1 and SHP-2 to block early signals mediated by FcεRI cross-linking. However, ligands for many of these receptors are yet to be identified.

Perspectives

Cell-cell communication is a crucial mode for multicellular organisms to accomplish complex biological functions and various signaling molecules have evolved to meet complicated demands to connect extracellular stimuli with intracellular components. Our tide model incorporates the majority, if not all, of immune cells in the context of an initiator and modulator concept to describe the rise of immune response to environmental stimuli due to transmission of primary and costimulatory signals while this response subsequently falls owing to the presence of coinhibitory signals. This process is reminiscent of the rise and fall of sea levels due to gravity forces by the sun, the moon, and the Earth's rotation. In addition to adaptive immunity, our model might better describe how innate cells trigger an inflammatory response and how these responses are regulated. Cosignaling molecules, whose expression is responsive to local environments, balance the communication between host innate cells and microorganisms. The intimate interaction between microorganisms and the host immune system covers a wide range of contacts, which are far beyond those between DAMPs and PRRs. Compared with infectious pathogens, commensal bacteria preferentially trigger inhibitory cosignals or fail to induce stimulatory cosignals directly or indirectly to host immune cells. It remains to be seen how each cosignal is induced or dampened to cooperate with PRRs, and in so doing combat infectious pathogens, or induce tolerance to commensal bacteria.

The same cosignaling molecule could be found on various immune cell types and execute the same or similar functions, dependent on receptor(s) or ligand(s) with which it could interact. This would allow maximal efficiency of immune responses to be initiated and expanded, leading to a highly coordinated response of multiple cell types. In this context, tight control from coinhibition becomes critical to tune down such responses in a certain level to prevent tissue or organ damage spanning from an acute inflammation to chronic autoimmunity.

It appears also important that one cell type possesses multiple cosignaling molecules. Cosignaling molecules for certain cell types usually come from one or two protein families and execute overlapping but not redundant roles. This cosignal mode could ensure that dysfunction of one cosignal could be offset by other cosignals, so that one cosignal defect would not lead to extreme immune dysfunction. At the same time, each cosignal with similar function could specialize in a certain step or type of immune response, thereby exploiting its unique expression profile, in terms of expression location, timing, and sensitivity to induction. On the other hand, the types of coreceptors are far broader than we originally thought, and many pathways from unrelated families could have similar regulatory function but use distinct signaling machineries. In that way, these cosignals could operate in parallel without any signaling disruption or conflict. Finally, the multiplicity of cosignals ensures that one pathogen cannot elude immune response simply by targeting one pathway.

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